Boehringer Ingelheim
Ben Venue Laboratories

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Ben Venue Laboratories, Inc.

Re: Docket 01P-0574/CP1 Amendment

April 3, 2002

Dear Sir or Madam:

The undersigned submits comments to the above-referenced petition and specifically in response to a letter dated February 14, 2002, submitted to this petition by Novartis Pharmaceutical Corporation (Novartis). In that letter, Novartis suggests that the original formulation of Sandostatin® Injection was withdrawn for reasons of safety and efficacy. Ben Venue Laboratories (Ben Venue) wishes to point out that it is unaware of any determination by the Food and Drug Administration that the original formulation of Sandostatin® Injection was withdrawn for safety or efficacy reasons.

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Background:

The petitioner (Ben Venue) submitted the above-referenced petition to request that the Commissioner of the Food and Drug Administration determine that a discontinued formulation of Sandostatin (Octreotide Acetate Injection) containing sodium chloride and a glacial acetic acid / sodium acetate buffer system was not voluntarily withdrawn for reasons of safety or effectiveness. Ben Venue also requested that the FDA determine that a generic product using the previous formulation would not be less safe or effective and would be therapeutically equivalent to the currently marketed innovator product. The request also asked that an ANDA for Octreotide Acetate Injection may reference the discontinued labeling that was previously approved by FDA.

Discussion:

The Food and Drug Administration maintains a list of drug products that are eligible for submission as abbreviated new drug applications. That list, referred to as the "Orange Book", contains all FDA-approved drug products. When reviewing the approved labeling for the

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reference-listed drug Sandostatin (NDA 19667), the currently approved formulation differs from the formulation originally approved. The current formulation differs in the tonicity agent and buffer system compared to the previously approved formulation. The key issue of Ben Venue's request related the use of sodium chloride as a tonicity agent. Sodium chloride was used in the withdrawn formulation. Since the regulations allow for ANDAs to propose the use of the same or different buffers compared to the reference-listed drug, it is believed that the buffer proposed by the ANDA applicant would be properly evaluated during the ANDA review process.

The regulations (21 CFR 314.94(a)(9)(iii)) govern inactive ingredients that may be contained in drug products approved pursuant to Section 505(j) of the Food, Drug and Cosmetic Act. These regulations specify the differences that are permitted for inactive ingredients contained in products submitted as ANDAs compared to those of the reference-listed drug product. Tonicity agents are one type of inactive ingredient that may not differ from the reference-listed drug. However, the petitioner proposes to utilize sodium chloride in its proposed product based on the previous finding by the Agency that the formulation of Octreotide Acetate Injection (Sandostatin) containing sodium chloride as a tonicity agency was safe and effective. The Novartis document raises numerous concerns related to its original buffer system and the glacial acetic acid / sodium acetate buffer system. It is important to point out that buffers are one type of inactive ingredient for parenteral products that can differ from the reference-listed drug. The ANDA applicant shall identify and characterize differences and provide information demonstrating that the differences do not affect the safety of the proposed product. Therefore, Ben Venue believes that its proposed formulation could contain a glacial acetic acid / sodium acetate buffer system because the Novartis formulation containing this buffer system was not withdrawn for safety or efficacy. Alternatively, Ben Venue could choose another buffer system in accord with 21 CFR 314.94(a)(9)(iii). The FDA will then evaluate the acceptability of the buffer system during the technical review of the ANDA.

As noted, Novartis marketed the original formulation without a change to the labeling that advised practitioners of additional warnings related to the original formulation. Likewise, the petitioner is unaware of any information, such as letters or other communications, directed to practitioners that the previous formulation raised safety concerns and that patients were at risk for use of the product. Finally, the petitioner

is unaware of any action taken by Novartis to immediately remove the previous formulation from the marketplace after the revised formulation was approved. Thus, it appears that at least one particular incentive for the new formulation relates to a controlling patent that covers the new formulation until 2015. Had it not been for this patent, the relevant patent for the old formulation expires in October 2002, clearing the way for ANDAs without concern for controlling patents. Thus, the new formulation affords an opportunity for exclusive marketing rights to a product that was otherwise deemed safe and effective by the FDA, with no evidence to the contrary.

Under FDA regulations, drugs are withdrawn from the list if the Agency withdraws or suspends approval of the drug application for reasons of safety or effectiveness, or if the FDA determines that the listed drug was withdrawn, discontinued from marketing, or withheld from sale for reasons of safety or effectiveness (21 CFR 314.162). The regulations also provide that the Agency must make a determination as to whether a listed drug is withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved [21 CFR 314.161(a)(1)]. Should the FDA determine that the original formulation was withdrawn from sale for safety or effectiveness reasons, the Agency will publish a notice of this decision in the Federal Register indicating that the original Sandostatin® Injection formulation was determined to be unsafe or ineffective.

Ben Venue wishes to acknowledge one error included in our original petition as pointed out by Novartis. Novartis is correct that Sandostatin® Injection may be administered subcutaneously.

Summary:

Based on available information, it does not appear that the original formulation of Sandostatin® Injection was withdrawn for safety or effectiveness reasons. Rather, the new formulation may provide slightly decreased pain on injection. It is disingenuous at best for Novartis to argue that the old formulation was unsafe given that the product was marketed with the old formulation from 1988 to 1996, an eight year period of exposure to patients, without any notification to practitioners that the product had an undesirable safety profile. Further, there is no evidence that Novartis took any action to remove the old formulation from the market upon approval of its modified formulation.

Because the regulations clearly permit the FDA to assess the potential impact on safety of proposed buffer systems contained in parenteral drug products submitted pursuant to ANDAs, difference in buffer systems, if any, will be carefully evaluated during the review process. Finally, Ben Venue does not believe that it is necessary to reference old labeling for Sandostatin® Injection in order to rely on a previously marketed formulation of the reference-listed drug, since a difference in inactive ingredients is clearly the type of labeling change that is contemplated and permitted by the regulations.

Respectfully submitted,

Molly Rapp
Regulatory Affairs
Ben Venue Laboratories, Inc.

cc: G. Buehler, R.Ph., Director, Office of Generic Drugs
D. Orloff, M.D., Director, Division of Endocrine and Metabolic Drug Products

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